

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Rubin et al.

Group Art Unit: 1652

Serial No. Not yet assigned

Examiner: Slobodyansky, E.

Filed: Herewith

Attorney Docket No. B97-081-7

For: *KUZ, a Novel Family of
Metalloproteases*

Date: May 31, 2001

This application is a divisional of USSN 09/709,126, filed Nov. 8, 2000, which is a divisional of USSN 09/285,502, filed Apr. 2, 1999, now Pat No 6,190,876, which is a divisional of USSN 08,937,931, filed Aug. 27, 1997, now Pat No 5,935,792 which is a continuing appln. of 60/053,476, filed Jul. 23, 1997 and 60/019,390, filed Aug. 29, 1996.

PRELIMINARY AMENDMENT

The Commissioner for Patents
Washington, DC 20231

Dear Commissioner:

Prior to examination of this application, please enter the following amendments:

IN THE SPECIFICATION

Please replace the paragraph beginning on line 6 of p.1 with the following:

This application is a divisional of USSN 09/709,126, filed Nov. 8, 2000, which is a divisional of USSN 09/285,502, filed April 2, 1999, now US Pat No. 6,190,876, which is a divisional of USSN 08/937,931, filed August 27, 1997, now US Pat No. 5,935,792, which claims the benefit of 60/053,476, filed Jul. 23, 1997 and 60/019,390, filed Aug. 29, 1996, each of which is incorporated by reference herein in its entirety.

Please replace the first paragraph following "BRIEF DESCRIPTION OF THE DRAWINGS" on p.3 with the following paragraph:

09871881-0000

Figure 1 (A). Sequence alignment of predicted KUZ proteins from *Drosophila* (DKUZ, SEQ ID NO:2), mouse (MKUZ, SEQ ID NO:8) and *Xenopus* (XKUZ, SEQ ID NO:10). The full length amino acid sequence of MKUZ was deduced from the nucleotide sequence of two overlapping cDNA clones. Partial amino acid sequence of XKUZ was deduced from the nucleotide sequence of a PCR product that includes parts of the disintegrin and Cys-rich domains. The alignments were produced using Geneworks software (IntelliGenetics). Residues identical among two species are highlighted. Predicted functional domains are indicated. Amino acid sequences from which degenerate PCR primers were designed are indicated with arrows. Orthologs of *kuz* are also present in *C. elegans* (GenBank accession nos. D68061 and M79534), rat (Z48444), bovine (Z21961) and human (Z48579).

At p.5, line 14, before the paragraph beginning "The subject domains...", please insert the following paragraph:

Ordinarily, the allelic variants, the conservative substitution variants and the members of the *kuz* family of proteins, will have an amino acid sequence having at least 75% amino acid sequence identity with one or more of the disclosed human full length, human secreted form, mouse and *Drosophila kuz* protein sequences, more preferably at least 80%, even more preferably at least 90%, and most preferably at least 95%. Identity or homology with respect to such sequences is defined herein as percentage of amino acid residues in the candidate sequence that are identical with the known peptides, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology, and not considering any conservative substitutions as part of the sequence identity. N-terminal, C-terminal or internal extensions, deletions, or insertions into the peptide sequence shall not be construed as affecting homology.

Please replace the paragraph bridging p.26 and 27 with the following paragraph:

Xenopus kuz was cloned by PCR using degenerate primers (XK1) and (XK4) which correspond to *Drosophila* KUZ sequence HNFGSPHD (SEQ ID NO:2, residues 609-616) and GYCDVF (SEQ ID NO:2, residues 870-875), respectively. First strand cDNA from stage 18

Xenopus embryos was used as template in a standard PCR reaction with an annealing temperature of 50°C. A PCR product of expected size was purified and used as template for another PCR reaction using a nested primer (XK3), corresponding to Drosophila KUZ sequence EECDCG (SEQ ID NO:2, residues 688-693), and XK4. The PCR product was subcloned into Bluescript and sequenced. Anti-sense RNA was used as a probe for whole mount *in situ* hybridization of Xenopus embryos according to standard procedures (Harland, R. (1991). Meth. Cell Biol. 36, 685-695).

At page 41, line 42, please insert the following text:

(2) INFORMATION FOR SEQ ID NO:9:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 486 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: cDNA
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

TACAGCGACC	AATGTAAGGA	TGAATGTTGC	TATGATGCCA	ATCAGCCAGA	AAACCTAAAG	60
TGCACATTAA	AGCCTGGAAA	ACAGTGCAGT	CCCAGCCAGG	GCCCTTGTTG	CACCACTGGA	120
TGTACCTTCA	AGCGAGCAGG	TGAGAACTGT	CGGGAGGAAT	CTGACTGTGC	CAAGATGGGA	180
ACTTGCAATG	GCAACTCTGC	TCAGTGTCCA	CCATCCGAAC	CAAGAGAGAA	CCTGACTGAG	240
TGTAACAGGG	CAACCCAAGT	TTGCATCAAG	GGGCAATGCT	CAGGATCTAT	CTGTGAGAGG	300
TATGACTTGG	AAGAGTGCAC	TTGCGGCAGT	ACTGATGAAA	AAGATGACAA	AGAGCTGTGC	360
CACGTTTGCT	GCATGGAGAA	AATGATACCG	CACACATGTG	CTAGCACTGG	TTCAGAAAGTA	420
TGGAAAGCTT	ACTTTAAAGG	AAAGACTATT	ACGTTACAAC	CAGGATCACC	TTGCAATGAA	480
TTTAAA						486

(2) INFORMATION FOR SEQ ID NO:10:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 162 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: peptide
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Tyr	Ser	Asp	Gln	Cys	Lys	Asp	Glu	Cys	Cys	Tyr	Asp	Ala	Asn	Gln	Pro
1			5					10					15		
Glu	Asn	Leu	Lys	Cys	Thr	Leu	Lys	Pro	Gly	Lys	Gln	Cys	Ser	Pro	Ser
			20					25					30		
Gln	Gly	Pro	Cys	Cys	Thr	Thr	Gly	Cys	Thr	Phe	Lys	Arg	Ala	Gly	Glu
			35				40					45			
Asn	Cys	Arg	Glu	Glu	Ser	Asp	Cys	Ala	Lys	Met	Gly	Thr	Cys	Asn	Gly
			50			55				60					
Asn	Ser	Ala	Gln	Cys	Pro	Pro	Ser	Glu	Pro	Arg	Glu	Asn	Leu	Thr	Glu
					70					75				80	
Cys	Asn	Arg	Ala	Thr	Gln	Val	Cys	Ile	Lys	Gly	Gln	Cys	Ser	Gly	Ser
			85					90						95	
Ile	Cys	Glu	Arg	Tyr	Asp	Leu	Glu	Glu	Cys	Thr	Cys	Gly	Ser	Thr	Asp
			100				105					110			
Glu	Lys	Asp	Asp	Lys	Glu	Leu	Cys	His	Val	Cys	Cys	Met	Glu	Lys	Met
			115				120					125			
Ile	Pro	His	Thr	Cys	Ala	Ser	Thr	Gly	Ser	Glu	Val	Trp	Lys	Ala	Tyr
			130			135					140				
Phe	Lys	Gly	Lys	Thr	Ile	Thr	Leu	Gln	Pro	Gly	Ser	Pro	Cys	Asn	Glu
145					150					155					160

IN THE CLAIMS

Please cancel all pending claims and enter new claims 14-33 as follows:

14. A composition comprising an antibody or antibody fragment which specifically binds a KUZ polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8.

15. A composition according to claim 14, wherein the amino acid sequence is residues 320-673 of SEQ ID NO:2.

16. A composition according to claim 14 wherein the amino acid sequence is residues 212-454 of SEQ ID NO:4.

17. A composition according to claim 14, wherein the amino acid sequence is SEQ ID NO:6.

18. A composition according to claim 14, wherein the amino acid sequence is residues 213-455 of SEQ ID NO:8.

19. A composition according to claim 14, wherein the amino acid sequence is SEQ ID NO:2.

20. A composition according to claim 14, wherein the amino acid sequence is SEQ ID NO:4.

21. A composition according to claim 14, wherein the amino acid sequence is SEQ ID NO:8.

22. A composition comprising an antibody or antibody fragment which specifically binds a dominant-negative mutant of a KUZ polypeptide, said mutant consisting of (a) an amino acid sequence selected from the group consisting of SEQ ID NO:2, 4 and 6, wherein the protease domain is deleted, or (b) SEQ ID NO:2, wherein glutamate at residue 606 is substituted with alanine.

23. A composition according to claim 14, wherein the antibody or fragment thereof specifically binds the extracellular domain of the KUZ polypeptide.
24. A composition according to claim 14, wherein the antibody or fragment thereof specifically binds the intracellular domain of the KUZ polypeptide.
25. A composition according to claim 14, wherein the antibody is, or the fragment is a portion of, a polyclonal antibody.
26. A composition according to claim 14, wherein the antibody is, or the fragment is a portion of, a monoclonal antibody.
27. A composition according to claim 14, wherein the antibody is, or the fragment is a portion of, a single-chain antibody.
28. A composition according to claim 14, wherein the antibody is, or the fragment is a portion of, a mouse antibody.
29. A composition according to claim 14, wherein the antibody is, or the fragment is a portion of, a human antibody.
30. A composition according to claim 14, wherein the antibody is, or the fragment is a portion of, a mouse-human chimeric antibody.
31. A composition according to claim 14, wherein the antibody or the fragment is labeled.
32. A composition according to claim 14, wherein the antibody or the fragment is fluorescently labeled.
33. A method for making an antibody according to claim 14, comprising the step of immunizing a

cell or animal with a polypeptide comprising an amino acid sequence selected from the group consisting of residues 320-673 of SEQ ID NO:2, residues 212-454 of SEQ ID NO:4, SEQ ID NO:6, and residues 213-455 of SEQ ID NO:8 or fragment thereof sufficient to elicit said antibody, whereby the antibody is elicited.

REMARKS

The enclosed specification is identical to the specification of the prior application 09/709,126. The foregoing amendments to the enclosed specification are identical to those made in 09/709,126 except for updating the cross-reference to related applications.

The new claims are directed to the antibody counterparts of the claims issued and allowed in 09/285,502 and 09/709,126, respectively. Claims 14-22 provide comparable limitations to those of claims 14-21 and 25 allowed in 09/709,126. Support for antibodies specific to the extracellular and intracellular domains of KUZ polypeptides is found on p.8, lines 15-17; support for polyclonal antibodies is found on p.8, lines 16-29; support for monoclonal antibodies is found on p.8, line 30 - p.9, line 16; support for single-chain antibodies is found on p.9, lines 17-19; support for KUZ-specific antibody fragments is found on p.9, lines 19-28; support for mouse antibodies is found on p.8, line 24; support for human antibodies is found on p.9, lines 7-11; support for chimeric antibodies is found on p.9, lines 11-15; support for fluorescently labeled antibodies is found on p.8, lines 7-10.

These amendments add no new matter.

The Examiner is invited to call the undersigned if she would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

The Commissioner is hereby authorized to charge any fees or credit any overcharges relating to this communication to our Deposit Account No. 19-0750 (order no. B97-081-7).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



Richard Aron Osman, Ph.D., Reg. No. 36,627
Tel: (650) 343-4341; Fax: (650) 343-4342

VERSION WITH MARKINGS TO SHOW CHANGES MADE

First paragraph following "BRIEF DESCRIPTION OF THE DRAWINGS" on p.3:

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